REMARKS

Claims 1-6 and 9-36 are pending in the present application. Claims 5-6 are rejected. Claims 7 and 8 are canceled. Claims 1-4 and 9-36 are withdrawn from consideration as being drawn to a non-elected invention. In the last Amendment and Response after Final Rejection, claim 5 was amended to recite the particular SEQ ID NOs. exemplified in the specification, and claim 6 was amended as requested by the Examiner to clarify the fusion protein.

As Applicants understand the Advisory Action mailed on September 29, 2006, the last Amendment and Response after Final Rejection mailed on September 13, 2006 was successful in overcoming all of the rejections except the rejection based upon enablement for failure to teach ***how to use*** the peptides.

Rejection under 35 USC 112, first paragraph

The Examiner maintains the rejection of claims 5-6 as not properly enabled based upon the rationale that the specification fails to teach "***how to use***" this broad genus of peptides. The rejection appears to be based upon the rationale that there is a large genus, there is no identification of a ligand for most of the peptide species, and there is no identification of a specific biological function for most of the peptide species. Further, the Examiner says that one of ordinary skill in the art would not know which bromodomain peptides would bind to which acetyl lysine containing peptides.

The legal test for determining enablement as regards "how to use"

A. Requires a finding of lack of "substantial utility" under 35 USC 101

Applicants respectfully contend that the Examiner's rejection is not properly based upon the law. Applicants respectfully ask the Examiner to again consider the law as expounded in MPEP 2107.01. A deficiency under the utility prong of 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. *See In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *In re Jolles*, 628 F.2d 1322, 1326 n.10, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971) ("If such compositions are in

fact useless, appellant's specification cannot have taught how to use them."). Courts have also cast the 35 U.S.C. 101/ 35 U.S.C. 112 relationship such that 35 U.S.C. 112 presupposes compliance with 35 U.S.C. 101. See *In re Ziegler*, 992 F.2d 1197, 1200-1201, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993) ("***The how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. 101 that the specification disclose as a matter of fact a practical utility for the invention. ... If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112.***"); *In re Kirk*, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) ("Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention."). For example, the Federal Circuit noted, "[o]bviously, if a claimed invention does not have utility, the specification cannot enable one to use it." *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). As such, ***a rejection properly imposed under 35 U.S.C. 101 for lack of utility should be accompanied with a rejection under 35 U.S.C. 112, first paragraph.*** It is equally clear ***that a rejection based on "lack of utility," whether grounded upon 35 U.S.C. 101 or 35 U.S.C. 112, first paragraph, rests on the same basis (i.e., the asserted utility is not credible).*** The MPEP states that to avoid confusion, any lack of utility rejection that is imposed on the basis of 35 U.S.C. 101 should be accompanied by a rejection based on 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection should be set out as a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. MPEP 2107.01 also indicates that a 35 U.S.C. 112, first paragraph, rejection should indicate that because the invention as claimed does not have utility, a person skilled in the art would not be able to use the invention as claimed, and as such, the claim is defective under 35 U.S.C. 112, first paragraph. ***A 35 U.S.C. 112, first paragraph, rejection based on lack of utility should not be imposed or maintained unless an appropriate basis exists for imposing a utility rejection under 35 U.S.C. 101.*** In other words, a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis is not proper unless a 35 U.S.C. 101 rejection is proper. ***In particular, the factual showing needed to impose a rejection under 35 U.S.C. 101 must be provided if a rejection under 35 U.S.C. 112, first paragraph, is to be imposed on "lack of utility" grounds.***

B. Experimentation to the point of "Undue Experimentation" is allowed

The legal test of enablement is clearly recognized as an analysis of whether an application, when filed, contained sufficient information regarding the subject matter of the claim as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision *of Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: ***is the experimentation needed to practice the invention undue or unreasonable?*** That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

C. Analogous circumstances have led to a finding of utility and hence "enablement"

As noted above, the factual showing needed to impose a rejection under** 35 U.S.C. 101 **must be provided if a rejection under** 35 U.S.C. 112, **first paragraph, is to be imposed on "lack of utility" grounds. "[A]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Fisher*, 421 F.3d at 1371, 76 USPQ2d at 1230.

Inventions asserted to have utility in the treatment of human or animal disorders are subject to the same legal requirements for utility as inventions in any other field of technology. *In re Chilowsky*, 229 F.2d 457, 461-2, 108 USPQ 321, 325 (CCPA 1956) ("There appears to be no basis in the statutes or decisions for requiring any more conclusive evidence of operativeness in one type of case than another. The character and amount of evidence needed may vary, depending on whether the alleged operation described in the application appears to accord with or to contravene established scientific principles or to depend upon principles alleged but not generally recognized, but the degree of certainty as to the ultimate fact of operativeness or inoperativeness should be the same in all cases"); *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967) ("***Thus, in the usual case where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry, operativeness is not questioned, and no further evidence is required.***"). ***As such, pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy** 35 U.S.C. 101.*

Courts have repeatedly found that ***the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and thus satisfies the utility requirement.*** As the Court of Customs and Patent Appeals held in *Nelson v. Bowler*:

> ***Knowledge of the pharmacological activity of any compound is obviously beneficial to the public.*** It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, ***we conclude that adequate proof of any such activity constitutes a showing of practical utility.***

Nelson had developed and claimed a class of synthetic prostaglandins modeled on naturally occurring prostaglandins. Naturally occurring prostaglandins are bioactive compounds that, at the time of Nelson's application, had a recognized value in pharmacology (e.g., the stimulation of uterine smooth muscle which resulted in labor induction or abortion, the ability to raise or lower blood pressure, etc.). To support the utility he identified in his disclosure, Nelson included in his application the results of tests demonstrating the bioactivity of his new substituted prostaglandins relative to the bioactivity of naturally occurring prostaglandins. The court concluded that Nelson had satisfied the practical utility requirement in identifying the synthetic prostaglandins as pharmacologically active compounds. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980).

In *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980), an inventor claimed protection for pharmaceutical compositions for treating leukemia. The active ingredient in the compositions was a structural analog to a known anticancer agent. The applicant provided evidence showing that the claimed analogs had the same general pharmaceutical activity as the known anticancer agents. The court reversed the Board's finding that the asserted pharmaceutical utility was "incredible," pointing to the evidence that showed the relevant pharmacological activity.

The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott [v. Finney]*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed.Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. ***The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.*** Accordingly, 35 U.S.C. 101, is not to be construed under

the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. *See, e.g., In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975).

These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. In such cases, the asserted utility is usually clear - the invention is asserted to be useful in treating the particular disorder. ***If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under*** *35 U.S.C. 101.*

D. Applicants have clearly demonstrated utility according to the requirements of the law

Applicants provided previously supplemental evidence regarding the bromodomains of other proteins. Applicants previously submitted that because teachings regarding the potential use of the P/CAF bromodomain are explicitly set forth, the requirements of the law as regards describing "how to use" are met. Applicants previously submitted the Declaration of Dr. Ming-Ming Zhou pursuant to 37 C.F.R. 1.132 wherein the Declarant clarified that he is aware of ***many proteins containing a bromodomain that have been shown to interact with other proteins***. Representative examples include the bromodomain of WSTF (Williams syndrome transcription factor) that interacts with lysine-acetylated histones (Fujiki, R., *et al., Ligand-induced transrepression by VDR through association of WSTF with acetylated histones.* Embo J, 2005); the bromodomain of the transcriptional cofactor p300 that binds to nucleosome (Ragvin, A., *et al., Nucleosome binding by the bromodomain and PHD finger of the transcriptional cofactor p300.* J Mol Biol, 2004. **337**(4): p. 773-88); the bromodomain of CBP/p300 that binds to acetylated MyoD (Polesskaya, A., *et al., Interaction between acetylated MyoD and the bromodomain of CBP and/or p300.* Mol Cell Biol, 2001. **21**(16): p. 5312-20); the bromodomain of NoRC (the SNF2h-containing chromatin-remodeling complex) that interacts with K16-acetylated histone H4 (Zhou, Y. and I. Grummt, *The PHD finger/bromodomain of NoRC interacts with acetylated histone H4K16 and is sufficient for rDNA silencing.* Curr Biol, 2005. **15**(15): p. 1434-8); the bromodomains of BDF1 and BDF2 that bind to histone H4 (Matangkasombut, O., *et al., Bromodomain factor 1 corresponds to a missing piece of yeast*

TFIID. Genes Dev, 2000. **14**(8): p. 951-62); the bromodomain of the WBSCR9 gene, encoding a novel transcriptional regulator, in the Williams-Beuren syndrome deletion at 7q11.23 (Peoples, R.J., *et al., Identification of the WBSCR9 gene, encoding a novel transcriptional regulator, in the Williams-Beuren syndrome deletion at 7q11.23.* Cytogenet Cell Genet, 1998. **82**(3-4): p. 238-46); the bromodomain-containing TIF1α: a possible link between KRAB zinc finger proteins and nuclear receptors (Le Douarin, B., *et al., TIF1alpha: a possible link between KRAB zinc finger proteins and nuclear receptors.* J Steroid Biochem Mol Biol, 1998. **65**(1-6): p. 43-50); and, the bromodomain of CBP that interacts with human tumor suppressor p53 at acetylated lysine 372 (Mujtaba, S., *et al., Structural mechanism of the bromodomain of the coactivator CBP in p53 transcriptional activation.* Mol Cell, 2004. **13**(2): p. 251-63). (*See*, Paragraph 5) In view of this wealth of information in the art, it is clear that one of skill in the art has a wealth of bromodomains at his or her disposal. As such, a skilled artisan may practice the invention without undue experimentation.

Dr. Ming-Ming Zhou, in the Declaration previously submitted pursuant to 37 C.F.R. 1.132, clarified that he is aware of ***many proteins containing a bromodomain that have been shown to interact with other proteins and for which the consequence of this interaction is understood as regards biological activity.*** Examples of these include that the bromodomain containing 2 (Brd2) is expressed in distinct patterns during ovarian folliculogenesis independent of FSH or GDF9 action (Trousdale, R.K. and D.J. Wolgemuth, *Bromodomain containing 2 (Brd2) is expressed in distinct patterns during ovarian folliculogenesis independent of FSH or GDF9 action.* Mol Reprod Dev, 2004. **68**(3): p. 261-8); the bromodomain of the MLL-CBP fusion protein is required for generating a myelodysplastic-like syndrome that evolves into myeloid leukemia (Lavau, C., *et al., Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia.* EMBO J., 2000. **19**: p. 4655-4664); the bromodomain-containing histone H3 acetylase dGcn5 is a key player in Drosophila melanogaster metamorphosis(Carre, C., *et al., The histone H3 acetylase dGcn5 is a key player in Drosophila melanogaster metamorphosis.* Mol Cell Biol, 2005. **25**(18): p. 8228-38); the bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription (Jang, M.K., *et al., The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent*

transcription. Mol Cell, 2005. **19**(4): p. 523-34); the PHD finger/bromodomain of NoRC interacts with acetylated histone H4K16 and is sufficient for rDNA silencing (Jang, M.K., *et al.*, *The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription.* Mol Cell, 2005. **19**(4): p. 523-34); the bromodomain-containing protein Bdf1p acts as a phenotypic and transcriptional multicopy suppressor of YAF9 deletion in yeast (Bianchi, M.M., *et al.*, *The bromodomain-containing protein Bdf1p acts as a phenotypic and transcriptional multicopy suppressor of YAF9 deletion in yeast.* Mol Microbiol, 2004. **53**(3): p. 953-68); Bdf1 bromodomains' interactions with acetylated H4 tails help anchor the transcriptional protein complex TFIID to the promoter during the initial stages of transcription activation (Martinez-Campa, C., *et al.*, *Precise nucleosome positioning and the TATA box dictate requirements for the histone H4 tail and the bromodomain factor Bdf1.* Mol Cell, 2004. **15**(1): p. 69-81); the CBP bromodomain and nucleosome targets are required for Zta-directed nucleosome acetylation and transcription activation (Deng, Z., *et al.*, *The CBP bromodomain and nucleosome targeting are required for Zta-directed nucleosome acetylation and transcription activation.* Mol Cell Biol, 2003. **23**(8): p. 2633-44); the bromodomains anchor chromatin-modifying complexes to promoter nucleosomes (Hassan, A.H., *et al.*, *Function and selectivity of bromodomains in anchoring chromatin-modifying complexes to promoter nucleosomes.* Cell, 2002. **111**: p. 369-379); the bromodomain mediates transcriptional intermediary factor 1alpha -nucleosome interactions (Remboutsika, E., *et al.*, *The bromodomain mediates transcriptional intermediary factor 1alpha -nucleosome interactions.* J Biol Chem, 2002. **277**(52): p. 50318-25). (*See*, paragraph 7)

Dr. Ming-Ming Zhou, in the Declaration pursuant to 37 C.F.R. 1.132, clarified that he is aware of ***many proteins that have been shown to interact with the bromodomain of another protein.*** Representative examples include nucleosomal core histones H3, H4, H2A and H2B, each of which has multiple known lysine acetylation sites. In addition, other proteins including cellular proteins of p53 (Mujtaba, S., *et al.*, *Structural mechanism of the bromodomain of the coactivator CBP in p53 transcriptional activation.* Mol Cell, 2004. **13**(2): p. 251-63); NF-κB (Greene, W.C. and L.F. Chen, *Regulation of NF-kappaB action by reversible acetylation.* Novartis Found Symp, 2004. **259**: p. 208-17; discussion 218-25) and HIF1α (Chun, Y.S., *et al.*, *Phorbol ester stimulates the nonhypoxic induction of a novel hypoxia-inducible factor 1alpha*

isoform: implications for tumor promotion. Cancer Res, 2003. **63**(24): p. 8700-7) interact with a bromodomain of another protein. (*See*, paragraph 6) In view of this wealth of information in the art, it is clear that one of skill in the art has a wealth of bromodomains and their corresponding ligand at his or her disposal. As such, a skilled artisan may practice the invention without undue experimentation. Further, Applicants have asserted a "substantial" and "credible" utility pursuant to the requirements of 35 USC 101 and its corollary 35 USC 112, first paragraph.

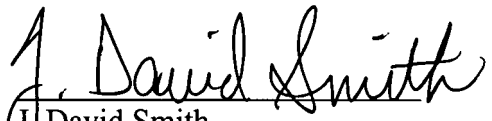
Fees

No fees are believed to be necessary in connection with this submission. If this is in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

CONCLUSION

Applicants believe that the claims are in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned the telephone number provided below.

Respectfully submitted,



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